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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,607	10/23/2001	Lino Tavares	208.1004US	1029

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EXAMINER
GHALI, ISIS A D

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 06/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,607	TAVARES ET AL.	
	Examiner	Art Unit	
	Isis Ghali	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-11,13-16,20-24,26,27,29-45* is/are pending in the application.

4a) Of the above claim(s) *39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-11, 13-16, 20-24, 26, 26, 29-38, 40-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The receipt is acknowledged of applicants' amendment and request for extension of time, both filed 03/15/2004.

Claims 3, 12, 17-19, 25, and 28 have been canceled. Claim 39 has been withdrawn from consideration.

Claims 1, 2, 4-11, 13-16, 20-24, 26, 27, 29-38, 40-45 are included in the prosecution.

Claim Rejections - 35 USC § 112

1. Claims 35 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 35, the expression "rubber-like polymer" does not set out the metes and bounds of the claim. Recourse to the specification does not define the expression "rubber-like polymer". Clarification is requested.

Claim 44 recites the limitation "softening ester" in claim 23. There is insufficient antecedent basis for this limitation in the claim.

Response to Arguments

Applicant's arguments filed 03/15/2004 have been fully considered but they are not persuasive.

Regarding the rejection of claim 35, applicants traverse the rejection by arguing that the "rubber-like synthetic polymers" are known by those skilled in the art, and disclosed by US '711.

In response to the above argument, the examiner agrees that the "rubber-like synthetic polymers" are known in the art, but the "rubber-like synthetic polymers" is broad class that encompasses wide varieties of polymers, copolymers and block polymers, and applicants did not disclose in the specification what specific "rubber-like synthetic polymers" are suitable for their invention.

Regarding claim 44, the listing of the claims submitted by applicants does not show replacing the word "ester" by "agent" as applicants assert.

Claim Rejections - 35 USC § 103

2. Claims 1, 2, 4-11, 13-16, 20-24, 26, 27, 29-38, 40-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,910,205 ('205).

US '205 teaches a transdermal delivery system of loratadine for the treatment of allergic conditions (abstract). The system is formed of patch applied to skin for a specific period of time to permit the penetration of a desired amount of loratadine through the

skin. The patch will be worn for one to four days and provides a total daily dose of 0.5 to 5 mg (col.2, lines 28-34). The patch comprises a reservoir having 10-20% loratadine; 50-60% solvent; and 20-35% fatty acid esters, i.e. softening agents (col.2, lines 19-29). The patch further comprises a backing layer and a release liner (col.2, line 64; col.3, line 6). The patch delivers 2.26 mg/15cm^2/day of loratadine (Table I). The reference disclosed that the dose may be varied depending on the size and age of the patient, and may also depends upon the severity of the condition being treated (col.3, lines 56-60). The frequency of dosage application can be once every 3 days once every 7 days (col.4, lines 5-10).

The reference does not teach the specific delivery profile of loratadine, the specific amounts of different ingredients, or specific solvents and softening agents in the transdermal delivery system.

The claimed amounts of different ingredients in the reservoir layer do not impart patentability to the claims because it is within the skill in the art to select optimal parameters in order to achieve a beneficial effect. Thus, the claimed amounts of the drug, solvent and the softening agent are not considered critical, absent evidence to the contrary.

The selection of particular solvent and softening agent for a specific drug is within the skill of the art depending on the properties of the each drug and its intended use. Thus the solvents and softening agents claimed in claims 37, 38, 44, and 45, do not impart patentability to the presented claims, absent evident to the contrary.

The determination of the relative release rate via an in-vitro permeation test utilizing a Valia-Chien cell is known in the art and it is not part of the claimed method of treating allergic rhinitis; or even a part of the transdermal device that provide particular plasma levels of loratadine. It is only an in-vitro diagnostic test that is expected to provide the same results obtained from two similar delivery devices tested under the same circumstances, and the recitation of this in-vitro test does not impart patentability to claims directed to method of treating allergic rhinitis or claims directed to transdermal device applied to patients to provide specific plasma levels of loratadine, i.e. in vivo use.

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a transdermal device to deliver loratadine to treat allergic conditions as disclosed by US '205, and adjust the dose to deliver a specific desired plasma profile according to the patient's need, motivated by the teachings of US '205 that the dose may be varied depending on the size and age of the patient, and may also depends upon the severity of the condition being treated, with reasonable expectation of having a transdermal drug delivery device that delivers loratadine at the desired levels and treats allergic conditions effectively.

Response to Arguments

Applicant's arguments filed 03/15/2004 have been fully considered but they are not persuasive. Applicants traverse the above obviousness rejection by arguing that there is no evidence that the disclosed transdermal systems were ever administered to human. The reference does not disclose steady state plasma level of loratadine from 1-

3ng/ml. There is no suggestion or motivation from the teaching of the reference to obtain the claimed steady state of plasma level of the drug.

In response to the above arguments, the examiner is pointing out to col.1, lines 46-53, where the reference teaches the systemic treatment of allergic reactions in mammals, and humans are mammalian species. The reference disclosed providing constant blood level of loratadine to the patient in need, as desired by applicants, col.2, lines 36-37. The patch delivers 2.26 mg/15 cm^2/day of loratadine, which is the same amount delivered by the instant patch. It is expected to obtain the same plasma level from the transdermal patch that deliver loratadine to the skin at the same rate. Determination of the drug dose is within the skill of the art and it is controlled by many variables such as age, weight, severity of the allergic reaction, etc. In response to applicant's argument that there is no suggestion to modify the reference, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one having ordinary skill in the art would have been motivated by the teachings of US '205 that the dose may be varied depending on the size and age of the patient, and may also depends upon the severity of the condition being treated, with reasonable expectation of having a transdermal drug

delivery device that delivers loratadine at the desired levels and treats allergic conditions effectively. In considering the disclosure of the reference, it is proper to take into account not only the specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom. *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968). The rational to modify or to combine the prior art does not have to be expressly stated in the prior art; the rational may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art.

3. Claims 1, 2, 4-11, 13-16, 20-24, 26, 27, 29-38, and 40-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,103,735 ('735) in view of US 5,091,186 (186).

US '735 teaches a pharmaceutical composition useful for treating allergic rhinitis comprising loratadine (abstract; col.5, line 66). The composition can be administered in the form of transdermal patches (col.7, lines 8-10).

The reference does not teach the specific delivery profile claimed by the applicants as claimed in claims 1-16. The reference does not teach the structure of the transdermal delivery system as claimed in claims 20-38 and 40-45.

US '186 teaches a transdermal drug delivery device to deliver drugs at therapeutically effective rates for about 20-28 hours (abstract; col.6, lines 4-20; col.7, lines 29-40). The reference teaches the antihistaminic as one of the drugs to be delivered by the transdermal delivery device (col.5, line 10). The transdermal device

comprises a flexible backing layer, an adhesive drug reservoir layer, and a release liner (col.3, lines 25-30, 6-63; col.4, line 43). The delivery profile of the drug is determined by the diffusivity of the drug in the reservoir layer, the solubility of the drug in the reservoir layer, and the degree of drug loading (col.6, lines 24-44). A given drug loading value will provide certain duration of delivery rate (col.7, lines 18022). To achieve the known desirable blood level of the drug, the delivery rate of the drug ranges from 10-50 ug/cm^2/hr (col.7, lines 47-51). The reservoir is pressure sensitive adhesive comprising rubbers, polysiloxane and polyurethanes (col.4, lines 33-40). The reservoir further comprises solvent and glycol, claimed by applicant as softening agent (col.6, line 1; col.7, line 55).

The claimed amounts of different ingredients in the reservoir layer do not impart patentability to the claims because it is within the skill in the art to select optimal parameters in order to achieve a beneficial effect. Thus, the claimed amounts of the drug, solvent and the softening agent are not considered critical, absent evidence to the contrary.

The selection of particular solvent and softening agent for a specific drug is within the skill of the art depending on the properties of the each drug and its intended use. Thus the solvents and softening agents claimed in claims 37, 38, 44, and 45, do not impart patentability to the presented claims, absent evident to the contrary.

The determination of the relative release rate via an in-vitro permeation test utilizing a Valia-Chien cell is known in the art and it is not part of the claimed method of treating allergic rhinitis; or even a part of the transdermal device that provide particular

plasma levels of loratadine. It is only an in-vitro diagnostic test that is expected to provide the same results obtained from two similar delivery devices tested under the same circumstances, and the recitation of this in-vitro test does not impart patentability to claims directed to method of treating allergic rhinitis or claims directed to transdermal device applied to patients to provide specific plasma levels of loratadine, i.e. in vivo use.

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention to treat allergic rhinitis using a transdermal device comprising loratadine, as disclosed by US '735, and provide the loratadine in the transdermal device disclosed by US '186 that provide a particular delivery profile of the drug, and manipulate the amount of the drug to obtain the desired delivery profile, motivated by the teaching of US '186 that a given drug loading value will provide a certain duration of delivery rate depending on the drug loading, with reasonable expectation of having a transdermal drug delivery device to deliver loratadine to treat allergic rhinitis effectively.

Response to Arguments

Applicant's arguments filed 3/15/2004 have been fully considered but they are not persuasive. Applicants traverse the above rejection by arguing that US '735 does not teach the delivery profile as claimed by applicants, and US '186 does not teach maintaining the patch attached to the skin for 3-5 days, but replacing the patch every day. No motivation to combine the references and their combination would have been resulted into transdermal system of loratadine for 24 hours. No teaching of the combined references of the steady state of plasma level of from 1-3 ng/ml.

In response to the above argument, the examiner position is one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The primary reference teaches the transdermal administration of loratadine to treat allergic rhinitis, and the secondary reference teaches a delivery profile that can be determined by the diffusivity of the drug in the reservoir layer, the solubility of the drug in the reservoir layer, the degree of drug loading that will provide certain duration of delivery rate. The reference further teaches that to achieve the known desirable blood level of the drug, the delivery rate of the drug ranges from 10-50 ug/cm^2/hr, as claimed by applicants. It is expected to obtain the same plasma level from the transdermal patch that deliver loratadine to the skin at the same rate. Determination of the drug dose is within the skill of the art and it is controlled by many variables such as age, weight, severity of the allergic reaction, etc. The burden is on applicants to show that maintaining the patch for several days is superior to its replacement every day in order to maintain the steady plasma level. In response to applicant's argument that there is no suggestion to modify the reference, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re*

Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case one having ordinary skill in the art would have been motivated to adjust the delivery rate to obtain the desired plasma level for the desired time motivated by the teaching of US '186 that a given drug loading value will provide a certain duration of delivery rate depending on the drug loading, with reasonable expectation of having a transdermal drug delivery device to deliver loratadine in a specific desired profile to treat allergic rhinitis effectively. In considering the disclosure of the reference, it is proper to take into account not only the specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom. *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968). The rational to modify or to combine the prior art does not have to be expressly stated in the prior art; the rational may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art.

4. Claims 37, 38, 44, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over US '205 in view of US 5,240,711 ('711).

The teachings of US '205 are discussed above.

The reference does not teach the specific solvents and softening agents and their amount.

US '711 teaches a transdermal drug delivery device for controlled delivery of drug comprising backing layer, polymeric reservoir and protective liner. The reservoir comprising: 20-90% of polymeric material, 0.1-20% of the drug, 0.1-30% softener, and

0.1-30% of solvent (abstract; col.1, line 64-67; col.4, line 23). The reservoir is pressure sensitive adhesive and contains rubber-like co-, homo-, or block-copolymers (col.3, lines 25-26). The solvents used include those contain at least one acidic group, monoesters of dicarboxylic acids, such as monoethyl glutarate (col.4, lines 13-16). The softeners include medium chain triglycerides of the caprylic/capric acids or coconut oil; and dodecanol (col.3, lines 63-68; col.4, lines 1-2; col.7, lines 25-29). The backing is flexible, inflexible or aluminum foil (col.7, lines 5-12).

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention to treat allergic conditions using a transdermal device comprising loratadine that provides a specific delivery profile and having particular structure as disclosed by US '205, and select the specific solvents and softening agents disclosed by US '711, motivated by the teaching of US '711 that the transdermal device having these particular ingredients in its reservoir layer provides a controlled delivery of the drug, with reasonable expectation of having a transdermal drug delivery device to deliver loratadine to treat allergic conditions effectively.

Response to Arguments

Applicant's arguments filed 03/15/2004 have been fully considered but they are not persuasive. Applicants traverse the above rejection by arguing that US '711 only teaches buprenophine transdermally, thus, one skilled in the art would not modify US '205 with US '711 in order to formulate loratadine transdermal delivery system.

In response to the above argument, the examiner position is US '711 is relied upon for the solely teaching of the solvents and softening agents that are known in the art and widely used in conventional transdermal devises for controlled release of the drugs. In considering the disclosure of the reference, it is proper to take into account not only the specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom. *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968). The rational to modify or to combine the prior art does not have to be expressly stated in the prior art; the rational may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art.

5. Claims 37, 38, 44, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over US '735 in view of US '186 as applied to claims 1-16, 20-38 and 40-45 above, and further in view of US '711.

The teachings of US '735, US '186 and US '711 are discussed above.

The combination of US '735 and US '186 does not teach the specific solvents and specific softening agents as claimed in claims 37, 38, 44, and 45.

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention to treat allergic rhinitis using a transdermal device comprising loratadine that provides a specific delivery profile and having particular structure, and select the specific solvents and softening agents disclosed by US '711, motivated by the teaching of US '711 that the transdermal device having these particular ingredients in its

reservoir layer provides a controlled delivery of the drug, with reasonable expectation of having a transdermal drug delivery device to deliver loratadine to treat allergic rhinitis effectively.

Response to Arguments

Applicant's arguments filed 03/15/2004 have been fully considered but they are not persuasive. Applicants traverse the above rejection by arguing that one skilled in the art would not have been motivated to combine the references to arrive at the claimed invention.

In response to the above argument, the examiner position is US '711 is relied upon for the solely teaching of the solvents and softening agents that are known in the art and widely used in conventional transdermal devises for controlled release of the drugs. In considering the disclosure of the reference, it is proper to take into account not only the specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom. *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968). The rational to modify or to combine the prior art does not have to be expressly stated in the prior art; the rational may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art.

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US 5,045,319 disclosed transdermal delivery system to deliver pharmaceuticals wherein the in-vitro release studies can be conducted using Valia-Chien diffusion cell.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis Ghali whose telephone number is (571) 272-0595. The examiner can normally be reached on Monday-Thursday, 7:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Isis Ghali
Examiner
Art Unit 1615

THURMAN K. PAGE
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